REMARKS

Claims 1-25 are pending. Claims 5, 7, 10-15, 17, and 19-25 have been canceled. Claims 3, 4, 8, 9 and 18 have been amended for clarity. Claim 1 has been amended to recite limitations of original claims 13 and 17, and the MTP inhibitor of original claim 21. Claim 16 has been amended to particularly point out further compounds, as previously recited in original claim 23. No new matter has been added.

Claims 26-28 are new. Support for claim 26 may be found for example, on page 17, paragraph 58 of the instant specification. Support for claim 27 may be found throughout the specification and claims as originally filed, for example, on page 17, paragraph 58; page 18, paragraph 63; page 16, paragraph 53, and page 26, Example 8. Support for claim 28 may be found throughout the specification and claims as originally filed, for example, original claim 16.

Amendment of the originally filed claims, or cancellation of any claims should in no way be construed as an acquiescence, narrowing, or surrender of any subject matter. The amendments are being made not only to point out with particularity and to claim the present invention, but also to expedite prosecution of the present application. Applicant reserves the option to prosecute the originally filed claims further, or similar ones, in the instant or subsequently filed patent applications.

Claim Rejections under 35 U.S.C. § 112, first paragraph

Claim 1, 3-18, 20, 24 and 25 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement because "the specification as original filed fails to provide sufficient written bases of any the agents demonstrating wherein possession of the use of the broad terms: a disorder associated with hyperlipidemia and/or hypercholesterolemia and a further lipid modifying agent." Applicant respectfully traverses this rejection.

However, solely to expedite prosecution of this application, claim 1 has been amended to recited a method of treating hyperlipidemia or hypercholestermia, diseases that are well known to those of skill in the art. Further, claim 16 has been amended to recite particular further

compounds. Support for such amendment may be found in e.g., original claim 23. Claims 20 and 24-25 have been canceled. Applicant therefore requests withdrawal of this rejection.

Claim Rejections under 35 U.S.C. § 102

Claims 1-4, 6-8, 14, 15, 17, 19 and 22 stand rejected under 35 U.S.C. 102(b) as being anticipated by Biller et al., US 5,739,135. Applicant notes that independent claim 1 has been amended to include limitations of claim 5 and claim 13, which do not stand rejected under 35 U.S.C. 102(b) by Biller. Applicant therefore respectfully requests withdrawal of this rejection.

Claims 1-8, 14-16, and 18-23 stand rejected under 35 U.S.C. 102(b) as being anticipated by Gregg et al., US 5,883,109. Applicant notes that independent claim 1 has been amended to include limitations of claim 13, which do not stand rejected under 35 U.S.C. 102(b) by Gregg. Applicant therefore respectfully requests withdrawal of this rejection.

Claim Rejections under 35 U.S.C. § 103(a)

Claims 9-13, 17, 24 and 25 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Biller (U.S. 5, 739,135) ("Biller") or Gregg, U.S. Patent No. 6,057,339 ("Gregg") in view of Dow U.S. 6,194,454 ("Dow"). Applicant respectfully traverses this rejection in view of the following comments.

Applicant submits that the standard of obviousness requires a consideration of whether the subject matter, taken as a whole, would have been obvious at the time the invention was made to a person skilled in the art. As the Examiner knows, combining prior art methods to reach a conclusion of obviousness requires: (i) a finding that the prior art included each element claimed, (ii) a finding that one of ordinary skill in the art could have combined the elements by known methods and that in combination each element merely would have performed the same function as it did separately; and (iii) a finding that one of ordinary skill in the art would have recognized that the results of the combination were predictable.

Applicant first notes that claim 1 has been amended to recite a method that includes a specific dosing regimen. Neither Gregg nor Biller teach an effective method that includes, for example, initially administering a low dose of about 2 mg/day to about 13 mg/day, for about 1 to

about 4 weeks, and then an increasing second dose, and a third dose, as recited in claim 1. Rather, Biller, for example, teaches "5 to about 500 mg per day in single or divided doses of one to four times *daily*," with no teaching of an initial low dose level of 2 to 13 mg for 1 to 4 weeks as recited in claim 1.

Importantly, neither Gregg or Biller recognize that the disclosed MTP inhibitor would cause **two** significant adverse effects, gastrointestinal related disorders *and* increase in hepatic fat, when administered to patients only at a *constant* level. As a consequence, previous phase II trials in human patients, initially administering 25 mg/day of the claimed compound, were discontinued because of such adverse events. (See e.g. instant specification at e.g., paragraph 115; Example 8, and the accompanying Declaration of William Sasiela Ph.D. (the "Declaration"). Further, neither the Gregg or Biller reference recognize that the instantly claimed method would result in the reduced incidence of both of these adverse events, while still being efficacious. There is no guidance in Biller or Gregg to select, without undue experimentation, the claimed low initial dose from the very broad range of disclosed dose levels **–a range that spans 1 to 2 orders of magnitude-**, and then a step-wise increase in dose levels, to arrive at the instantly claimed method effective in significantly reducing adverse effects.

For example, Applicants note that there is no reasonable expectation that one skilled in the art at the time of the instant invention would arrive at the claimed method. For example, the disclosure recognizes that the method provides for possible adaptation by the liver to the claimed MTP inhibitor once administered at a low dose level of the claimed MTP inhibitor, and such an initial low dose may continue to limit e.g. hepatic steatosis (fatty liver) even when the patient is ultimately administered a higher dose, as described in the instant specification for example, at page 26 paragraph 115. Further, as noted in the specification, it had been previously concluded, after a patient study using constant dose levels of 25 mg per day, (that the claimed MTP inhibitor *could not* be developed as a drug for large scale use in the treatment of hypercholesterolemia. (Specification, paragraph 33).

The accompanying Declaration indicates that others of skill in the art, including the scientists and investigators of the failed trial, did not appear to arrive at any solution these adverse events, and that the instant invention is non-obvious as to these prior art teachings.

Further, Applicants note, as described in the accompanying Declaration, that the instantly claimed method, e.g. with an initial administration of about 5 mg/day for four weeks, and then step-wise increases to larger doses, results in dramatic difference in the rate of gastrointestinal (GI) effects as compared to a *constant* dose level administration of the claimed inhibitor- even when the constant dose level is substantially less than the dose administered after several step wise increases as instantly claimed. This significant reduction in GI effects is obtained even when patients also receive a further lipid modifying compound such as ezetimibe.

In contrast, Gregg teaches starting with low dose *combinations* of MTP inhibitors and other cholesterol lowering agents, effectively teaching away from the claimed method of the low step wise dose levels of the MTP inhibitor and a constant level of another agent, e.g. ezetimibe.

Applicants submit that the standard of obviousness requires a consideration of whether the subject matter, *taken as a whole*, would have been obvious at the time the invention was made to a person skilled in the art. Without conceding any prima facie case of obviousness, Applicant believes that the Office must consider any rebuttal evidence, including showings that the claimed invention possesses superior properties, as described in the accompanying Declaration.

Applicant notes that claims 24 and 25 have been canceled. The Dow reference appears to be cited as possibly relevant only to those claims. Applicants assert that nothing in the Dow reference teaches or suggests any element of the instant claims.

Applicant submits that the above references, either alone or in combination, fail to teach or suggest the claimed subject matter taken as a whole. In particular, the references alone or in combination, do not teach every limitation of the claims. Nor does the combination of each element of the claims merely perform the same function as it does separately. Further, there is no finding that one of ordinary skill in the art would have recognized that the results of the combination were predictable. Therefore, Applicant respectfully requests withdrawal of this rejection.

Any questions raised by this submission may be directed to the undersigned at (617) 570-8743. The Commissioner is hereby authorized to charge any underpayments, or credit any overpayments, to our Deposit Account No. 07-1700**, Reference: AGP-002**.

Respectfully submitted,

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